efficacy as relaxin in preventing deposition of extracellular matrix molecules by human fibroblast cells (see specification at 40 et seq.), and in stimulating cAMP production by normal human endometrial cells (see specification at 42). Moreover, Applicants made the surprising discovery that relaxin like factor acts *synergistically* with relaxin to promote softening of pubic ligaments in an *in vivo* mouse assay (see specification at 42-43). Thus, Applicants have demonstrated by way of actual working examples, both *in vitro* and *in vivo*, the medically relevant uses of relaxin like factor.

II. THE AMENDMENTS

With this Preliminary Amendment, Applicants have amended Claims 4, 15, and 16, without prejudice, for the purpose of more clearly defining what the Applicants regard as the invention and for placing the claims in condition for allowance. The amendments are fully supported by the specification and claims as originally filed. For example, Claim 4 has been amended to remove the claim limitation of preventing a condition susceptible to treatment with relaxin merely to simplify the issues for examination as suggested by the Examiner. Support for the amendment to Claim 4 can be found, for example, in the specification at page 5, lines 29-34, and at page 15, lines 6-8. Claim 15 has been amended to more clearly point out and distinctly claim the subject matter that the Applicants regard as their invention. Support for the amendment to Claim 15 can be found, for example, in the specification at page 9, lines 32-36. Claim 16 has been amended to correct a minor spelling error. The amendments do not constitute new matter. Therefore, entry of this Preliminary Amendment is respectfully requested.

III. REJECTION UNDER 35 U.S.C. § 112, First Paragraph

Claims 4-6 and 14-19 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which is not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. The rejections have been obviated in part by amendment and are traversed in part.

A. The argument of the examiner

Several arguments are made in an effort to support the alleged lack of enablement of the claims. First, although the Examiner acknowledges that the specification is

"fully enabled" for RLF maintaining sperm mobility, inhibiting collagen production *in vitro*, inhibiting fibronectin production *in vitro*, activating the expression of procollagenase, and pubic ligament softening in mice, the Examiner objects that the Applicants allegedly have not submitted any art that would indicate that these *in vitro* functions are well established and well correlated indications for concluding effectiveness to treat cardiovascular and neurological diseases. The Examiner also objects that the Applicants allegedly have not described with which cardiovascular disorders and neurological disorders relaxin like factor can be associated. Finally, the Examiner states that the extent to which the disorders are discussed is a conclusion from the activity of relaxin. The Examiner objects that relaxin is a structurally distinct peptide and that it is improper to conclude that the activity associated with a structurally distinct compound would also be associated with relaxin like factor.

B. The *functional* relationship between relaxin like factor and relaxin enables one of reasonable skill in the art to use relaxin like factor to treat the claimed disorders

Applicants respectfully submit that the specification fully enables the scope of the claims. First, the Examiner's assertion that the Applicants have extrapolated the function of relaxin like factor from relaxin based on structure is not accurate. Applicants respectfully submit that the Examiner is ignoring the most important and most surprising aspects of the invention. Applicants agree with the Examiner's observation that relaxin like factor and relaxin are structurally distinct peptides. In fact, as pointed out by the Examiner, relaxin like factor is more closely related *structurally* to insulin than it is to relaxin. Were the Applicants to extrapolate a function for relaxin like factor based merely on *structural* similarities, as alleged by the Examiner, the function ascribed to relaxin like factor might resemble the function of insulin. However, the Applicants were surprised to find that *functionally* relaxin like factor was closely related to relaxin, not insulin.

The functional similarities between relaxin like factor and relaxin were established by a number of experiments. Relaxin like factor binds to a relaxin receptor, but not the insulin receptor (see specification at page 33-36). Relaxin like factor also induces similar cellular responses as does relaxin including the maintenance of sperm motility (see specification at 36-38), the inhibition of collagen synthesis (see specification at 38-40), the inhibition of fibronectin synthesis (see specification at 40-41), and the stimulation of procollagenase synthesis (see specification at 41). Most significantly, relaxin like factor acts

synergistically with relaxin to stimulate cAMP release by human endometrial cells *in vitro* (see specification at 42) and to promote the softening of pubic ligaments in a mouse *in vivo* assay (see specification at 42-43). This *functional* relationship between relaxin like factor and relaxin is a basis of the invention and one of many bases for the treatment of the diseases with relaxin like factor recited in Claims 4-6 and 14-16.

Furthermore, the *synergistic* effects of relaxin like factor on relaxin *in vitro* and *in vivo* enables one of ordinary skill in the art to recognize that any condition susceptible to treatment with relaxin can show a synergistic response to simultaneous treatment with relaxin and relaxin like factor. Such conditions can be identified in the course of routine experimentation. In accord with *In re Angstadt*, the relevant inquiry for enablement under § 112, first paragraph, is whether the experimentation needed to test the effectiveness of a method is undue, requiring ingenuity beyond that of one of ordinary skill in the art. Examples of conditions susceptible to treatment with relaxin include, but are not limited to, scleroderma (see http://www.connetics.com/connxn_scl.html), peripheral vascular disease (see http://www.connetics.com/connxn_pvd.html), infertility (see http://www.connetics.com/connxn_inf.html), depression (see U.S. patent No. 5,753,623), sinus bradycardia (see U.S. patent No. 5,478,807), acute and chronic heart failure (see U.S. patent No. 5,166,191), neurodegenerative diseases (see U.S. patent No. 5,478,807), and hair loss (see concurrently filed application entitled "Method for Treatment of Hair Loss", Serial No. 08/473,516). Other conditions susceptible to treatment with relaxin include arteriosclerosis and vascular diseases, ischemia and thrombosis, hypertension, pregnancy's gestosis, allergic disorders, and inflammatory disorders (see U.S. patent No. 5,952,296). Further conditions include fibromyalgia, myofascial pain syndrome, chronic fatigue syndrome, dystonia, pelvic floor dysfunction, and irritable bowel syndrome (see U.S. patent No. 5,863,552 and U.S. patent No. 5,707,642).

C. Applicants have enabled the full scope of the claims, methods of treating a mammal for a condition susceptible to treatment with relaxin

Another objection raised by the Examiner is that the Applicants have allegedly not described which neurological and cardiovascular diseases are susceptible to treatment with relaxin like factor. The Examiner alleges that the scope of the claims include neurodegenerative and neurological disease, depression, hair loss, and cardiovascular diseases. However, Applicants respectfully note that claims 4-6 and 14-16 do not recite the

treatment of any and all diseases or even the treatment of any and all neurological, cardiovascular, depression, or hair loss diseases as implied by the Examiner. Rather, claim 4 and dependent claims 5-6 and 14-16 recite methods for treating a mammal *for a condition susceptible to treatment with relaxin*. As discussed above, one of ordinary skill in the art could determine conditions susceptible to treatment with relaxin like factor based on those conditions that are susceptible to treatment with relaxin in the course of ordinary experimentation. Furthermore, independent claim 17, and dependent claims 18 and 19, do not even recite treatment of the specific disorders cited by the Examiner. Applicants submit that when the proper scope of the claims is considered, the claims are fully enabled as discussed above.

D. The *in vivo* and *in vitro* results disclosed in the specification enable one of skill in the art use relaxin like factor to treat the claimed disorders

Finally, the Examiner invites the Applicants to submit art to show that the *in vitro* and *in vivo* results of the specification are well established and well correlated tests for concluding effectiveness to treat cardiovascular and neurological disorders. Specifically, the Examiner acknowledges that the specification is fully enabled for treatment with relaxin like factor for maintaining sperm mobility *in vitro*, inhibiting collagen production *in vitro*, inhibiting fibronectin production *in vitro*, activating the expression of procollagenase, and pubic ligament softening in mice, and invites the Applicants to submit art to show that these results are well established tests for concluding the effectiveness to treat cardiovascular and neurological disorders. Although Applicants believe that the specification fully enables the treatment of the claimed disorders as discussed above, Applicants do note that several patents and publications show that the *in vitro* and *in vivo* results described for relaxin like factor are indeed well correlated indications for the prevention and treatment of the claimed disorders.

First, relaxin like factor decreases the expression of collagen by human fibroblast cells independently and synergistically with relaxin (see specification at 40), independently decreases fibronectin expression by human fibroblasts (see specification at 40-41), and independently stimulates procollagenase expression by human fibroblasts (see specification at 41). The inhibition of collagen and fibronectin expression and the stimulation of procollagenase expression in fibroblasts *in vitro* are established tests for showing *in vivo* effectiveness for the treatment of lung diseases characterized by fibrosis. Unemori et al. examined the ability of relaxin to alter the connective tissue phenotype of human lung

fibroblasts *in vitro* and *in vivo*. They found that relaxin decreases procollagen and fibronectin overexpression in human lung fibroblasts *in vitro* and can inhibit lung fibrosis in a murine model. From these results, they concluded that relaxin can provide a means to regulate excess collagen deposition in lung diseases characterized by fibrosis (see Unemori et al., J. Clin. Invest. 98:2739-2745). In another study, Unemori et al. describe previous *in vitro* results including relaxin's ability to decrease the expression of interstitial collagens by human dermal fibroblasts in culture and relaxin's induction of an increase in the synthesis of collagenase. These results led them to evaluate the possibility that relaxin can decrease collagen accumulation *in vivo*. They found that relaxin indeed decreases active collagen accumulation *in vivo* and concluded that relaxin can be useful as a collagen-modulating agent in diseases such as scleroderma (see Unemori, et al., J. Invest. Dermatol. 101:280-285, copy enclosed). Given the disclosures of these two publications and the ability of relaxin like factor to reduce collagen and fibronectin expression and its ability to stimulate procollagenase expression, one of skill in the art would recognize the effectiveness of relaxin like factor to treat conditions susceptible to treatment with relaxin including diseases related to uncontrolled or abnormal collagen or fibronectin formation.

Second, relaxin like factor specifically binds to the relaxin receptor (see specification at 34-36). Specific binding of the relaxin receptor is an established indication for *in vivo* effectiveness for the treatment of cardiovascular diseases including bradycardia. For instance, U.S. patent No. 5,166,191 claims the use of relaxin in cardiovascular therapy. This use of relaxin are based on the "finding that relaxin binds specifically and with high affinity to receptors in the cardiac atria of both male and female rats" (see U.S. patent No. 5,166,191 at col. 5, lines 47-50). Similarly, U.S. patent No. 5,478,807 claims the use of relaxin in the treatment of bradycardia. This use of relaxin is also based on the "finding that relaxin binds specifically and with high affinity to receptors in the cardiac atria of both male and female rats" (see U.S. patent No. 5,478,807 at col. 5, lines 47-50). As a result, one of skill in the art would recognize that the specific binding of the relaxin receptor by relaxin like factor indicates that relaxin like factor would be effective for treating conditions susceptible to treatment with relaxin including cardiovascular disease and bradycardia.

Third, relaxin like factor specifically binds the relaxin receptor and binds to membrane preparations from mouse brain (see specification at 34-36). U.S. patent application Serial No. 07/902,637 (PCT US92/06927) discloses methods of treating

neurodegenerative diseases. These methods are based on the observation that relaxin binding sites are present in the brain and that relaxin mRNA is localized in the brain (see WO 93/03755 at 27-28). U.S. patent No. 5,753,623 claims methods for treating depression. These methods are based, in part, on the observation of relaxin receptors in the brain and the presence of mRNA for relaxin in the brain (see U.S. patent No. 5,753,623 at col. 1, line 67, to col. 2, line 4). Given the disclosures of U.S. Serial No. 07/902,637 and U.S. patent No. 5,753,623, one of skill in the art would recognize that the specific binding of the relaxin receptor by relaxin like factor and the binding of mouse brain membrane tissue by relaxin like factor indicate that relaxin like factor would also be effective in treating neurodegenerative or neurologic disease and depression that are susceptible to treatment with relaxin.

Fourth, relaxin like factor was as effective as relaxin in maintaining sperm motility (see specification at 36-38). In a review of experimental results involving the function of relaxin in the male, Weiss notes that relaxin stimulates sperm motility from suboptimal sperm samples and that it increases sperm penetration into oocytes. From these results, Weiss concludes that relaxin might be an effective therapeutic against male infertility (see Weiss, Biol. Reprod. 40:197-200, copy enclosed). One of skill in the art would combine the knowledge of the Weiss publication with the observation that relaxin like factor maintains sperm motility like relaxin to conclude that relaxin like factor can also be an effective therapeutic against male infertility.

Several *in vivo* effects of relaxin are correlated with defined *in vitro* activities of relaxin. Treatment of diseases related to uncontrolled or abnormal collagen or fibronectin formation is correlated to relaxin's ability to decrease collagen and fibronectin synthesis *in vitro* and relaxin's ability to increase collagenase synthesis *in vitro*. Treatment of cardiovascular disease, treatment of bradycardia, treatment of neurodegenerative and neurologic disease, and treatment of depression are all correlated with the specific binding of relaxin and the relaxin receptor. Finally, treatment of infertility is correlated with the ability of relaxin to maintain sperm motility *in vitro*. Since Applicants have demonstrated that relaxin like factor has these *in vitro* activities, Applicants submit that the specification fully enables methods of treating a mammal with relaxin like factor for conditions susceptible to treatment relaxin including cardiovascular disease, neurodegenerative or neurologic disease, sinus bradycardia, depression, diseases related to uncontrolled or abnormal collagen or fibronectin formation, and infertility.

E. Conclusion

In conclusion, Applicants submit that the specification fully enables methods of using relaxin like factor for the treatment of diseases susceptible to treatment with relaxin because of the similarity in function of relaxin like factor and relaxin, the synergistic effects of relaxin like factor on relaxin, and the series of *in vitro* and *in vivo* tests of the specification that demonstrate *in vivo* effectiveness for the treatment of the claimed diseases. Applicants therefore submit that the rejection of claims 4-6 and 14-19 under 35 U.S.C. § 112, first paragraph, for failing to enable the treatment of the disorders listed by the Examiner is inappropriate and request that it be withdrawn.

IV. THE REJECTION UNDER 35 U.S.C. § 112, Second Paragraph

Claim 15 has been rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention. Applicants have amended Claim 15 to recite a method of treatment of a mammal for a condition susceptible to treatment with relaxin by administering a therapeutically effective amount of relaxin like factor wherein the condition is ameliorated by softening the pubic ligament or the cervical ligament of the mammal. One of skill in the art would recognize the anatomical meanings of the terms "pubic ligament" and "cervical ligament." Based on Example 6.10 at pages 42-43 of the specification, one of skill in the art would also readily understand that the term "softening" indicates a widening of the distance between the interpubic bones of the mammal. The Examiner has also acknowledged that the specification is "fully enabled" for pubic ligament softening in mice. Since the claim as amended particularly points out and distinctly claims the subject matter of the invention, it is no longer indefinite, and the rejection is obviated. Applicants respectfully request that the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

V. CONCLUSION

Applicants respectfully submit that Claims 4-6 and 14-20 meet all the requirements for patentability and are in condition for allowance. An early indication of the same is therefore solicited.

No fee is believed due in connection with this response. However, should the Commissioner determine otherwise, he is authorized to charge any underpayment or credit any overpayment to Pennie & Edmonds LLP Deposit Account No. 16-1150. A copy of this sheet is enclosed.

Respectfully submitted,

Date: April 3, 2000

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